Ablett & Stebbing

CHARTERED PATENT ATTORNEYS
EUROPEAN PATENT ATTORNEYS
REGISTERED TRADE MARK

CAPARO HOUSE
101-103 BAKER STREET
LONDON W1M 1FD

TEL: 020 7935 7720
FAX: 020 7935 7790
E-MAIL: INFO@ABSTEB.CO.UK
WEB PAGE: WWW.ABSTEB.CO.UK

G.K. ABLETT B.Sc., CPA, EPA, MITMA
S.J. SUÈR B.Eng., CPA, EPA, MITMA

assisted by
KATRINA PEEBLES B.Sc., M.Sc.
R.S. FENDER B.Sc., Ph.D.
CARRIE ALLEN M.Chem.

consultants
P.J.H. STEBBING B.Sc., M.Sc., CPA, EPA, MITMA, FRSA
R.G. MARSH B.Tech., CPA, EPA, RTMA

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European Patent Office
Branch at the Hague
Receiving Section
PB 5818 Patentlaan 2
2280 HV Rijswijk (ZH)
The Netherlands

BY FACSIMILE AND POST

Dear Sirs,

PCT Patent Application No. PCT/GB99/04027
Applicant: Aberdeen University and The Common Services Agency for the Scottish Health Service
Short title: Allo-Reactive T-Cell Epitopes

We refer to the Written Opinion dated 4 October 2000 and the one month extension for responding thereto. We enclose herewith amended pages 27 to 29, in triplicate, to replace pages 27 to 31 currently on file. The claims have been amended to emphasise that the claimed subject matter relates to the tolerisation of a subject to an immunologically effective epitope or immunologically effective analogue or derivative thereof. We refer the Examiner to the disclosure of the entire application, in particular page 4 lines 15 to 32, for the basis for this amendment.

We note that the Examiner has raised an objection to the novelty and the inventiveness of the subject matter in the present invention on the basis of a document entitled "Identification of T-cell epitopes on the Rhesus Polypeptides in Autoimmune Haemolytic Anaemia" (D1) and an abstract entitled "Mapping Alloreactive T-cell epitopes on the Rhesus D Protein" (D2).

D1 relates to the disease autoimmune haemolytic anaemia (AIHA). In many patients with AIHA, autoantibodies can be demonstrated that target the Rh protein complex, including the RhD protein, but anti-D-specific antibodies are not a feature of this disease. In this connection, autoantibodies with other specificities are also frequently present. In this regard, the cause of autoimmune diseases is unknown but it is thought to be multifactorial and polygenic. In many cases autoimmune diseases show spontaneous exacerbations and remissions. The standard treatment

diseases show spontaneous exacerbations and remissions. The standard treatment for AIHA, as for most autoimmune disease, is administration of steroids which suppress the immune system. The same drugs are used to prevent graft rejection. As can be seen from the abstract of D1, the aim of D1 was to determine whether activated T cells from patients with AIHA mount recall responses to epitopes on Rhesus polypeptides. Further it was discussed whether or not AIHA resulted from activated T cells responsive to Rh polypeptides (see page 2712 col 2). In fact, it was shown that although T cells in the blood from patients with AIHA were responsive to Rh peptides, in three case there was no detectable Rh-specific antibody response and in two other cases the autoantibody was too weak to be defined. In this connection, D1 shows that even after extensive research it is still not known what triggers AIHA or how the body attacks itself. Accordingly, there is no disclosure or suggestion of a definition of a treatment for any alloimmune disease.

D2 is an abstract of a poster that was displayed at a meeting of the American Society for Haematology, drawing attention to the potential for a safe method of alloimmunising donors for the production of anti-RhD immunoglobulin. At present, to produce anti-RhD immunoglobulin, RhD positive red cells are injected into male or female RhD negative donors. Although anti-RhD antibodies are effectively produced, the donors risk contracting blood-born diseases which cannot be screened for before administration of the RhD positive red cells, for example vCJD. Accordingly, the authors of the paper of D2 were concerned with developing a safe synthetic method of stimulating anti-RhD immunologlobulins in donors.

The present application in contrast relates to the discovery that administration of an immunologically effective tolerising epitope of a rhesus protein or an immunologically active analogue or derivative thereof can result in the prevention of alloimmunisation of a subject or the immunosuppression of a response elicited by a subject who has previously been alloimmunised. Alloimmunisation can occur, for example, when a RhD negative woman is carrying a RhD positive fetus. In this connection, if during the pregnancy the woman's blood is in contact with blood from the fetus it is likely that she will raise an antibody response to the RhD protein in the blood of the fetus. Accordingly, in subsequent pregnancies, if the woman has not been treated with anti-RhD immunoglobulin from donors (see D2 above), RhD antibodies from the woman can cross the placenta, and may result in fetal death if it is RhD positive. The present application discloses a system which will result in the RhD negative woman tolerating the introduction of RhD protein antigens into her body, such that no RhD antibodies will be produced. Accordingly, in the future it will not be necessary to administer anti-RhD immunoglobulins to women at periods of time that it is likely that they will come in contact with their fetus' RhD positive blood. As will be appreciated, use of the present invention also has safety implications in that the anti-RhD immunoglobulin donors will no longer be required. In addition, it will be safer for the women and their fetuses because no episodes of contamination of the women's blood with RhD protein will be missed. There is also the possibility of reversing rather than preventing alloimmunisation by the administration of tolerogenic peptides to individuals who already produce anti-D.

The present application is novel over D1 because D1, as discussed above, relates

to an autoimmune disease which has a totally different pathogenesis, diagnosis, treatment and management from an alloimmune disease. In addition, D1 does not disclose the use of immunologically effective epitopes as a method of treating AIHA by tolerisation never mind a disease which has been caused as a result of alloimmunisation of a subject.

The present application is novel over D2 because, as discussed above, D2 relates to the production of epitopes for the stimulation of production of anti-RhD immunoglobulins in donors whereas the present application relates to the tolerisation of patients to alloantigens on the administration of immunologically effective epitopes (i.e the purpose of the epitopes in the present invention is to suppress production of anti-RhD immunoglobulins, not stimulate production thereof).

The disclosure in D2 is hence contraindicative to the presently claimed invention. A skilled person in the art reading D2 would consider that on administration of synthetic epitopes of the RhD protein to a subject, who is RhD negative, stimulation of anti-RhD antibodies would occur. Accordingly, if the same person was trying to suppress an immune response to RhD in pregnant RhD negative women, for example, they would not follow the teachings of D2 because the teachings of D2 imply that the immune response would be simulated not suppressed. As it will be appreciated, the stimulation of an immune response in a RhD negative women pregnant with a RhD positive fetus could have fatal consequences.

The Examiner has also suggested that the present invention lacks inventive step in view of a combination of D1 and D2. We would, in this connection, firstly question the validity of combining D1 and D2 to attack the present invention.

As set out in Rule 65.1 of PCT Regulations 2000 and EPC Guidelines Part C Chapter IV paragraph 9.7, documents should not be combined unless it would be obvious to a person skilled in the art that the disclosures in the documents should be combined. In this connection, a person skilled in the art would not combine the disclosures of D1 and D2 because D1 and D2 are papers from different and distinct fields of medical science. In this connection, D1 relates to the field of autoimmunity and D2 relates to the field of transfusion medicine.

The field of autoimmunity comprises many different diseases which effect many different tissues, organ or cells. Each of the diseases and has its own clinical spectrum. In most cases the pathogenesis of each disease is unknown and the antigens involved are not clearly identified. Accordingly, researchers in this field often concentrate on animal models of these diseases, investigating the T-cell and B-cell responses, and it remains to be demonstrated how the findings in these models can be applied to human autoimmune diseases.

The field of transfusion medicine is a smaller more select field which relates to the study of alloantibodies raised to circulating blood cells (red cells, white cells and platelets). In contrast to the field of autoimmunity the blood group antigens and their antibodies are well defined. Researchers in this field are knowledgeable about antibodies and their detection but have at best limited exposure to T-cell immunology.

This said, even if the teachings of D1 and D2 were combined, one would still not arrive at the present invention, since neither discloses the concept of tolerisation with an immunologically effective epitope of a rhesus protein as set out in the present invention. As such the person skilled in the art, supposedly of no imagination, would have to make this step themselves. We would contend that this is only possible using an undue degree of hindsight showing that the presently claimed invention is inventive over the combined disclosures of D1 and D2.

In support of the novelty and non-obviousness of the presently claimed invention over the disclosures of D1 and D2 on their own and in combination, it should moreover be noted by the Examiner that the development of anti-RhD immunoglobulins for the passive immunisation of women to prevent alloimmunisation started in the 1960s when the technique of providing anti-RhD immunoglobulins, as set out above was developed. However, there has been no significant improvement since then of the treatment or prevention of alloimmunisation even though it was known that there were considerable risks to, for example, anti-RhD immunoglobulins donors. Accordingly, whilst there has been a long felt need for the present invention, no one has achieved a solution until the present invention.

With regard to the objection raised in paragraph 2.1 of the Written Opinion, it is contended that the terms "analogue" and "derivative" are widely used in the art and therefore a person skilled in the art would understand what is intended by the terms and how to obtain analogues and derivatives of the epitopes. In this connection, an "analogue" of an epitope means any epitope which is produced by replacing at least one amino acid in the original epitope, which is recognised by the same T-cells as the original epitope, but which may have different effects on these T-cells from those exerted by the original epitope. A "derivative" of an epitope is the product after the original epitope has been modified (e.g placing glycosylated chain on at least one of the amino acids).

With regard to the objection raised in paragraph 2.2 of the Written Opinion the peptides have now be referred to by way of their Seq. ID numbers. On a related matter, it has come to the applicants' attention that a typographical error has occurred in the sequence listing. In this connection, the entry 223 on pages 1 to 13 should read RhCE (R2 cE) instead of RhCE (R2 CE) see Table 1 as filed. Accordingly, we enclose herewith amended sequence listing pages 1 to 13 to replace the like numbered pages currently on file. We also enclose herewith an amended sequence listing diskette.

With regard to the objection raised in paragraph 2.3 of the Written Opinion new claims 8 to 11 (old claims 13 to 16) have been reworded to refer to a pharmaceutical composition.

In light of the above we look forward to receiving a favourable International Preliminary Examination Report.

Yours faithfully,

SUÈR; Steven Johannes
Authorised Representative

Enc. Amended pages (x3)
Sequence listing pages (x3)
Sequence listing disk